Clinical correlates and outcome associated with changes in 6-Minute Walking Distance in Patients with Heart Failure

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Table 1. Characteristics of 1,714 patients who performed baseline 6MWT by 6MWT tertiles

6MWT (tertiles)	≤240 m	241-360 m	>360 m	p-value
N.	591	586	537	
Age (years)	73 ± 10	67 ± 12	62 ± 11	<0.001
Male sex	374 (63%)	453 (77.3%)	465 (86.6%)	<0.001
Inpatient visit	391 (66%)	329 (56.1%)	252 (46.9%)	<0.001
BMI (Kg/m^2)	27.8 ± 5.4	27.5 ± 4.9	27.7 ± 4.8	0.68
Heart rate (bpm)	82 ± 19	79 ± 19	79 ± 21	0.002
SBP (mmHg)	125 ± 21	125 ± 20	126 ± 20	0.92
Pulmonary rales	345 (59.2%)	278 (48.5%)	157 (30.3%)	<0.001
Peripheral edema	343 (68.2%)	271 (55.2%)	167 (39.2%)	<0.001
Elevated JVP	127 (32.6%)	95 (23.2%)	72 (18.6%)	<0.001
NYHA class III/IV	421 (72.3%)	312 (54.4%)	203 (38.1%)	<0.001
Orthopnea	196 (33.3%)	150 (25.6%)	105 (19.6%)	<0.001
LVEF (%)*	30 (25-38)	30 (25-35)	30 (25-35)	<0.001
LVEF >40%	74 (12.5%)	40 (6.8%)	23 (4.3%)	<0.001
Ischemic HF	295 (49.9%)	256 (43.7%)	195 (36.3%)	<0.001
PCI or CABG	223 (37.7%)	192 (32.8%)	151 (28.1%)	0.003
HFH in the last 12 months	228 (38.6%)	193 (32.9%)	162 (30.2%)	0.009
Atrial fibrillation	299 (50.6%)	246 (42.0%)	217 (40.4%)	<0.001
Previous stroke	61 (10.3%)	40 (6.8%)	33 (6.1%)	0.018
Peripheral arterial disease	73 (12.4%)	42 (7.2%)	45 (8.4%)	0.006
Hypertension	404 (68.4%)	380 (64.8%)	307 (57.2%)	<0.001
Device therapy	151 (25.5%)	133 (22.7%)	113 (21.0%)	0.19
Current smoking	73 (12.4%)	78 (13.3%)	80 (14.9%)	0.005
Diabetes	238 (40.3%)	173 (29.5%)	132 (24.6%)	<0.001
COPD	138 (23.4%)	90 (15.4%)	64 (11.9%)	<0.001
Malignancy	25 (4.2%)	15 (2.6%)	9 (1.7%)	0.032
Hemoglobin (g/dL)	12.7 ± 1.8	13.3 ± 1.8	13.9 ± 1.6	<0.001
eGFR (ml/min/1.73m2)	56.9 ± 21.5	64.8 ± 23.6	72.3 ± 21.1	<0.001
Serum Urea (mmol/L)	15.8 ± 10.3	13.3 ± 10.8	12.2 ± 8.8	<0.001
Serum Sodium (mmol/L)	139.1 ± 4.1	139.4 ± 3.5	140.0 ± 3.1	<0.001
Serum Potassium (mmol/L)	4.2 ± 0.6	4.2 ± 0.5	4.3 ± 0.5	0.66
Plasma Glucose (mmol/L)	7.2 ± 3.1	6.9 ± 2.9	6.7 ± 2.4	0.047
Total cholesterol (mmol/L)	4.1 ± 1.37	4.4 ± 1.3	4.5 ± 1.2	<0.001
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	0.52
NT-pro BNP (NPX)	3.3 ± 1.3	2.7 ± 1.3	2.4 ± 1.1	<0.001
TnI (pg/mL)*	14.5 (7.8-33.2)	11.1 (6.3-23.8)	8.3 (5.0-15.7)	<0.001
MRA	289 (49.1%)	327 (55.8%)	302 (56.2%)	0.019
Loop diuretics	590 (>99%)	582 (>99%)	534 (>99%)	0.40
Digoxin	110 (18.6%)	108 (18.4%)	102 (19.0%)	0.97
Beta-blocker	475 (80.4%)	513 (87.5%)	465 (86.6%)	0.001
Beta-blocker >=50% at 3 mo.	196 (33.2%)	222 (37.9%)	223 (41.5%)	0.014
ACEi/ARB	408 (69.0%)	449 (76.6%)	418 (77.8%)	0.001
ACEi/ARB >=50% at 3 mo.	282 (47.7%)	324 (55.3%)	342 (63.7%)	<0.001
6MWT (meters)*	154 (100-200)	310 (280-337)	422 (390-475)	-

Legend: BMI, body mass index; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HFH, heart failure hospitalization; COPD, chronic

obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker. *median (pct_{25-75}).

Table 2. Multivariable linear regression for baseline 6MWT (m) as dependent variable

Continuous 6MWT (baseline)	Std. beta-coefficient	Std. Err.	P-value
Age (per 10 yr)	-33.0 (-39.2 to -26.7)	3.2	<0.001
Male sex	59.2 (43.1 to 75.3)	8.2	<0.001
Inpatient	-68.4 (-85.6 to -51.2)	8.8	<0.001
Heart rate (per 10 bpm)	-6.1 (-9.5 to -2.7)	1.7	<0.001
NYHA III/IV	-58.9 (-75.2 to -42.6)	8.3	<0.001
Orthopnea	-31.5 (-47.6 to -15.4)	8.2	<0.001
Ischemic heart disease	-32.8 (-47.3 to -18.3)	7.4	<0.001
Previous stroke	-37.2 (-60.6 to -13.7)	11.9	0.002
Current malignancy	-46.2 (-83.9 to -8.6)	19.2	0.016
Serum Sodium (per 1 mmol/L)	4.0 (2.3 to 5.7)	0.9	<0.001
NT-proBNP (per NPX doubling)	-12.4 (-18.0 to -6.9)	2.8	<0.001
LogTnI (per each Log10)	-28.8 (-42.2 to -15.5)	6.8	<0.001

Model adjusted R^2 =0.35

Constant = 147.6

The standardized (std.) beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.

Table 3. Cox-proportional hazards models investigating the relationship between baseline 6MWT and outcome

HFH or Death	N. (%) of events	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Continuous 6MWT (m)					
Per each 50m less	641 (37.4%)	1.19 (1.15-1.22)	<0.001	1.08 (1.04-1.11)	<0.001
Tertile 6MWT (m)					
>360 m	118 (22.0%)	Reference	-	Reference	-
241-360 m	210 (35.8%)	1.85 (1.47-2.31)	<0.001	1.44 (1.14-1.80)	0.002
≤240 m	313 (53.0%)	3.07 (2.48-3.79)	<0.001	1.73 (1.38-2.18)	<0.001
Death	N. (%) of events	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Continuous 6MWT (m)					
Per each 50m less	385 (22.5%)	1.25 (1.19-1.30)	<0.001	1.14 (1.09-1.18)	<0.001
Tertile 6MWT (m)					
>360 m	57 (10.6%)	Reference	-	Reference	-
241-360 m	109 (18.6%)	1.88 (1.37-2.60)	<0.001	1.49 (1.08-2.06)	0.016
≤240 m	219 (37.1%)	4.11 (3.08-5.50)	<0.001	2.41 (1.76-3.29)	<0.001

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).

Total n. =1,714; Tertile n. ≤240m =591; 241-360m =586; >360m =537.

Table 4. Logistic regression of association between 6MWT and likelihood of titration of disease-modifying therapy to >50% of guideline-recommended target doses

Treatment up-titration	OR (95%CI)*	p-value
ACEi/ARB or β-blocker ≥50%		
Continuous 6MWT (m)		
6MWT per each 50m decline	0.91 (0.85-0.97)	0.002
Tertile 6MWT (m)		
>360 m	Reference	-
241-360 m	0.66 (0.47-0.92)	0.014
≤240 m	0.63 (0.43-0.92)	0.016
ACEi/ARB ≥50%		
Continuous 6MWT (m)		
6MWT per each 50m decline	0.95 (0.90-1.01)	0.052
Tertile 6MWT (m)		
>360 m	Reference	-
241-360 m	0.76 (0.56-1.02)	0.075
≤240 m	0.75 (0.54-1.04)	0.088
β-blocker ≥50%		
Continuous 6MWT (m)		
6MWT per each 50m decline	0.91 (0.85-0.96)	0.001
Tertile 6MWT (m)		
>360 m	Reference	-
241-360 m	0.85 (0.63-1.16)	0.31
≤240 m	0.66 (0.46-0.94)	0.022

*Adjusted on the "best" up-titration prediction model including: age, sex, race, heart failure duration, heart failure hospitalization in the previous year, heart failure of ischemic etiology, diabetes mellitus, hypertension, body mass index, systolic blood pressure, heart rate, left ventricular ejection fraction, NT-pro BNP, and estimated glomerular filtration rate.

Table 5. Logistic and linear regression for the association of medication up-titration with 6MWT change in meters (from baseline to 9-months)

Logistic regression for 6MWT change as categorical variable				
Up-titration	6MWT decrease*	6MWT increase	OR (95%CI)	P-value
ACEi/ARB or BB ≥50%	339 (71.8%)	889 (71.3%)	0.97 (0.77-1.23)	0.83
ACEi/ARB ≥50%	266 (56.4%)	705 (56.5%)	1.01 (0.81-1.25)	0.95
Beta-blocker ≥50%	200 (42.4%)	497 (39.9)	0.90 (0.73-1.12)	0.34
Linear regression for 6MWT change as continuous variable				
Up-titration	6MWT change : beta coefficient (95%CI)		Std. error	P-value
ACEi/ARB or beta-blocker ≥50%	4.42 (-13.78 to 22.63)		9.28	0.63
ACEi/ARB ≥50%	2.78 (-13.80 to 19.37)		8.46	0.74
Beta-blocker ≥50%	-7.21 (-23.95 to 9.53)		8.54	0.40

Legend: 6MWT, 6-minute walking test distance in meters; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; *6MWT decrease group includes 0 *i.e.*, no change.

The standardized beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.

Table 6. Cox-proportional hazards models investigating the relationship between 6MWT distance change from baseline to 9 months and outcome

HFH or Death	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Per each 50m decrease (continuous)	1.09 (1.06-1.12)	<0.001	1.09 (1.06-1.12)	<0.001
6MWT (decrease vs. increase)	1.56 (1.30-1.85)	<0.001	1.54 (1.30-1.85)	<0.001
Death	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Per each 50m decrease (continuous)	1.09 (1.04-1.14)	<0.001	1.09 (1.04-1.14)	<0.001
6MWT (decrease vs. increase)	1.59 (1.20-2.08)	<0.001	1.64 (1.25-2.13)	<0.001

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).